How to perform a Safety Evaluation – Risk Assessment on Extractables & Leachables

PDA TRAINING COURSE
EXTRACTABLES – LEACHABLES
VENICE
21 - 22 MARCH, 2019

Dr. Piet Christiaens

Topics Covered

- Basic Toxicological Principles dose response relationship
- Key Toxicological end-points
- General Impurity Qualification
- Solvents – Permissible Limits
- Mutagenic Impurities
- E&Ls
- Conclusions

THE DOSE-RESPONSE RELATIONSHIP

"The Dose Makes the Poison"
Paracelsius

THE DOSE-RESPONSE RELATIONSHIP

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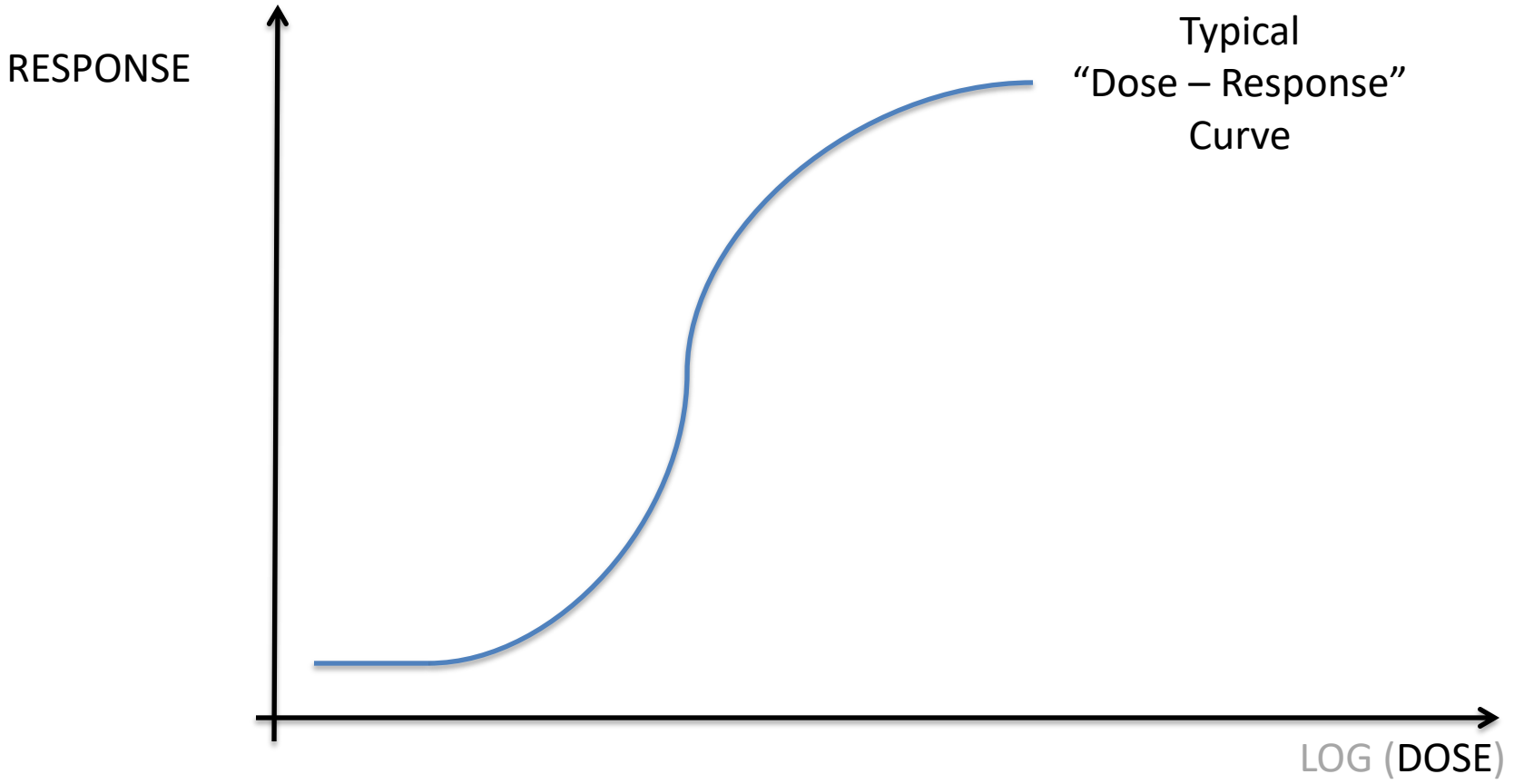
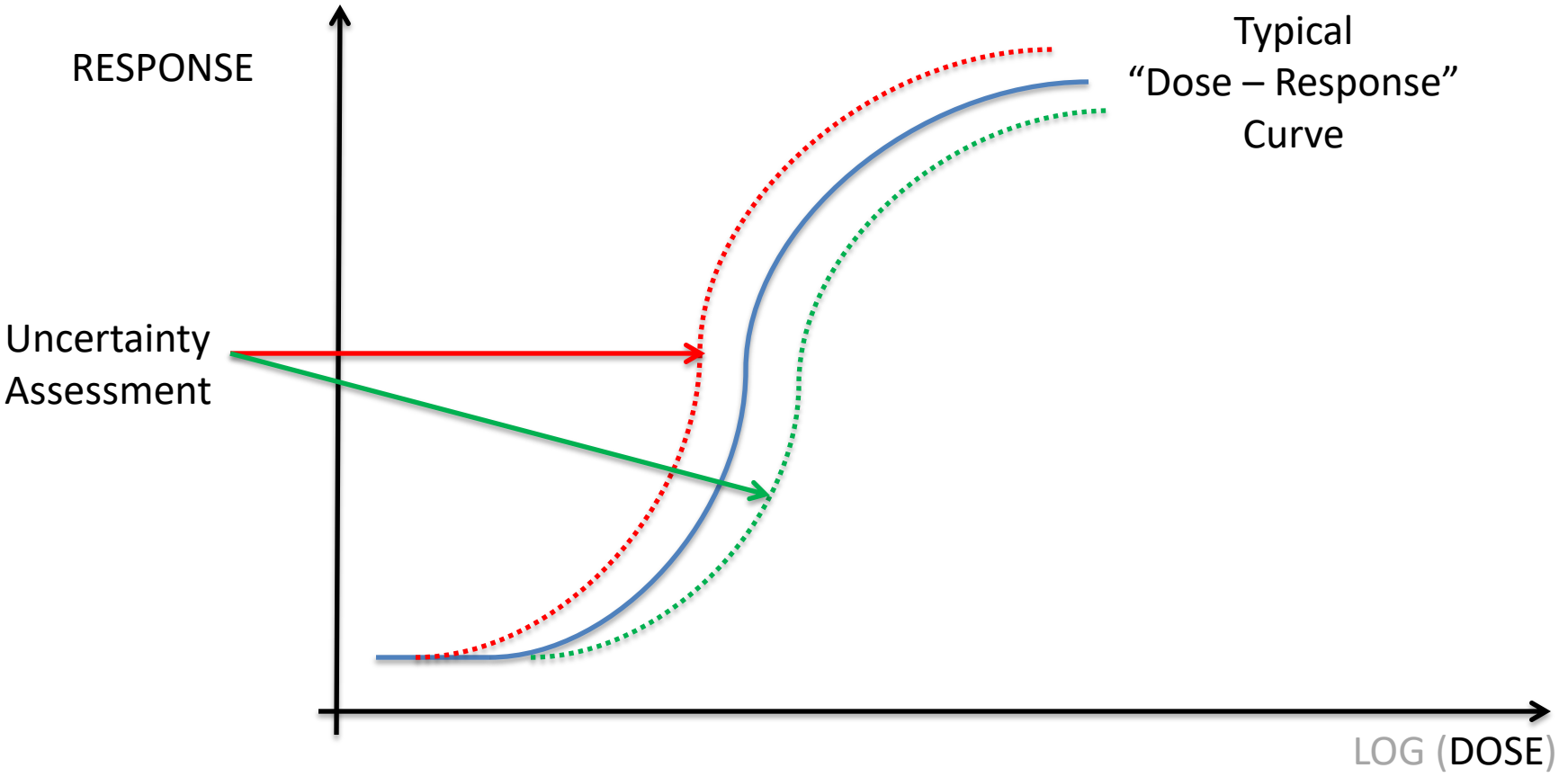


THE DOSE-RESPONSE RELATIONSHIP



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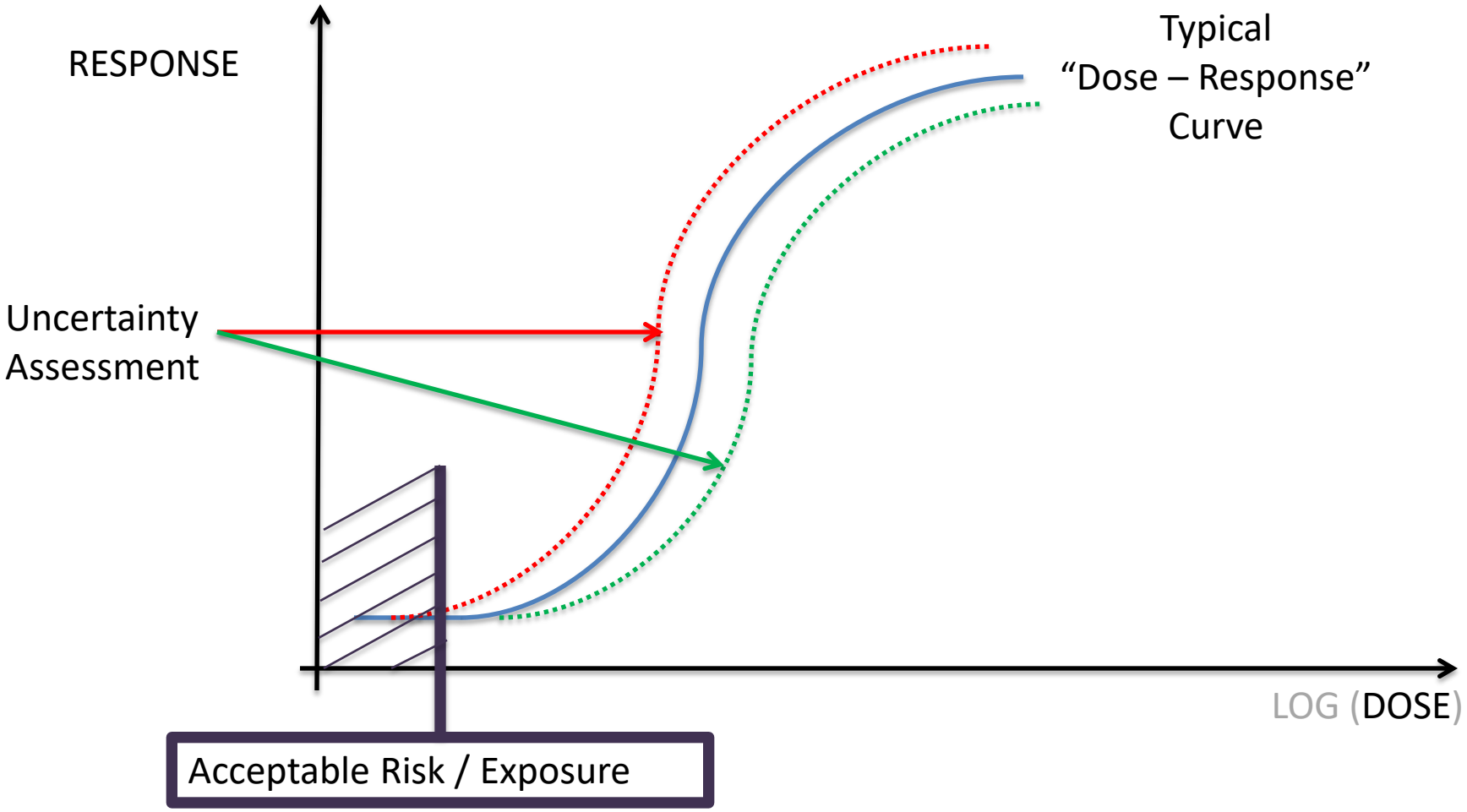
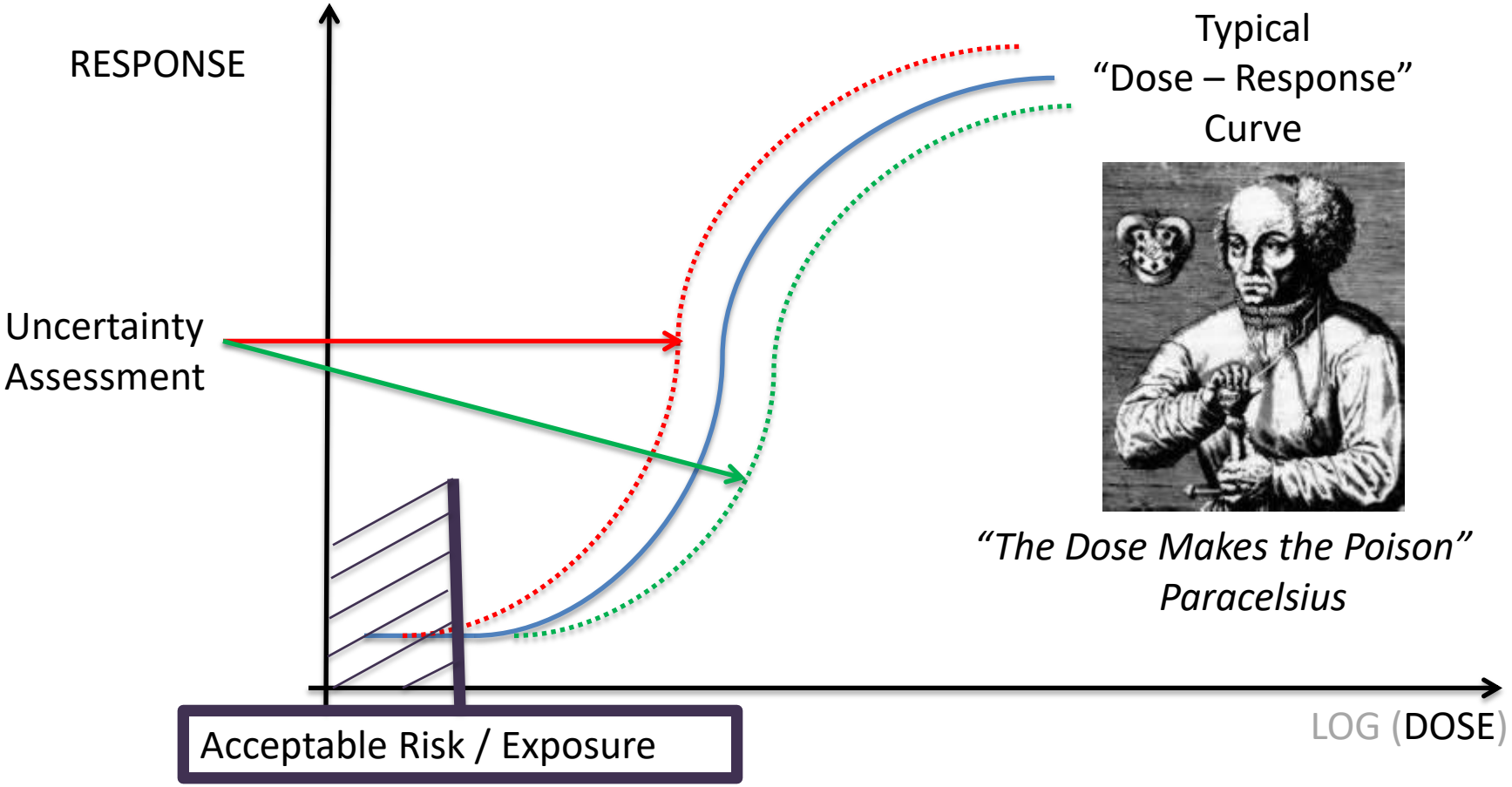
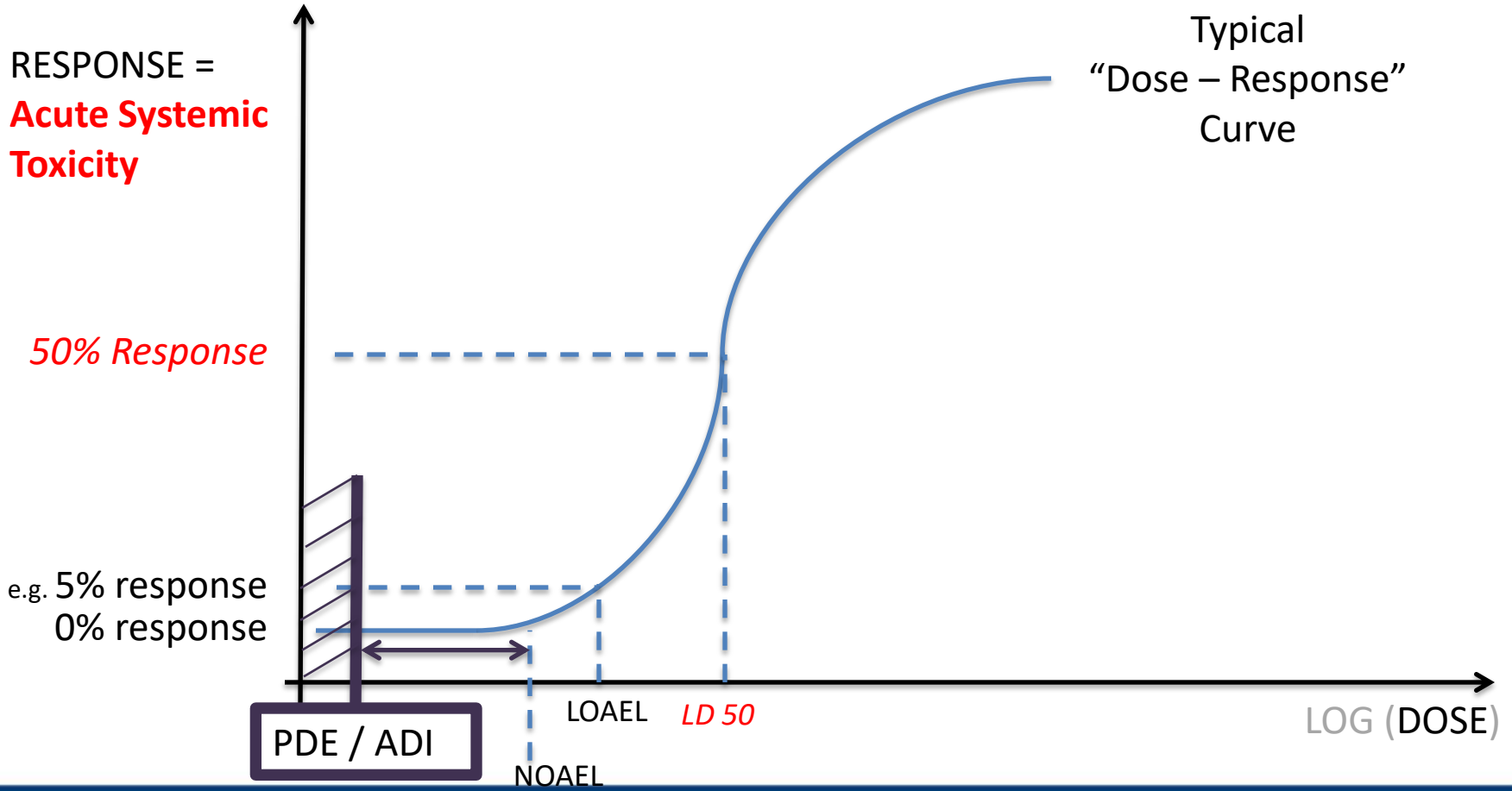


THE DOSE-RESPONSE RELATIONSHIP



THE DOSE-RESPONSE RELATIONSHIP

EXAMPLE: ACCUTE SYSTEMIC TOXICITY



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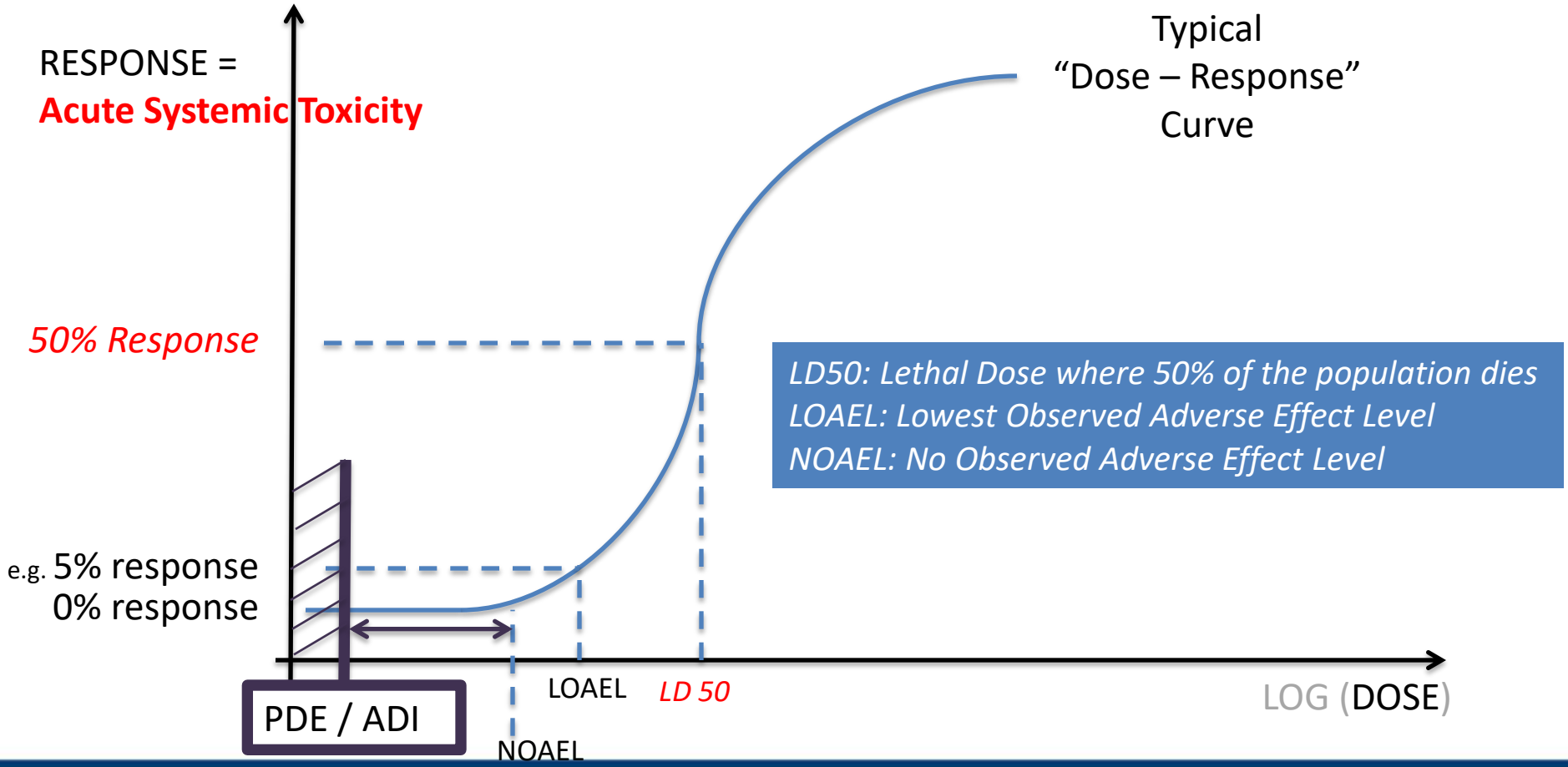


KEY ENDPOINTS

Toxicological endpoints to be considered (non – limitative):

Acute Systemic Toxicity → Often most readily available information (eg LD50, NOAEL, LOAEL,...)

Genotoxicity

Irritation

Sensitization

Reproduction Toxicity

Carcinogenicity

The "BIG FIVE"

Acute Systemic Toxicity

Definition:

Acute systemic toxicity testing is the **estimation** of the **human hazard potential** of a substance by determining its **systemic toxicity** in a test system (currently animals) following an **acute exposure**.

Source: alttox.org

Genotoxicity

Definition:

Genotoxicity is a broad term referring to **genetic damage**. This may be at a ***DNA level*** i.e. mutagenicity, or at a ***chromosomal level*** e.g. Clastogenicity / Aneugenicity.

This term has in the context of **ICH M7** been **replaced** by the more specific term mutagenicity that relates specifically to **DNA mutation**.

Irritation & Corrosion (e.g. Skin)

Definition:

Skin irritation and skin corrosion refer to **localized toxic effects** resulting from a **topical exposure of the skin to a substance.**

skin irritation is “the production of **reversible damage** to the skin following the application of a test substance for up to 4 hours

skin corrosion is “the production of **irreversible damage** to the skin; namely, visible **necrosis** through the epidermis and into the dermis, following the application of a test substance for up to 4 hours

Source: alttox.org

Sensitization (e.g. Skin)

Definition:

a *skin sensitizer* is “a substance that will induce an **allergic response following skin contact**”.

A substance is classified as a **skin sensitizer** when human data show it can **induce a sensitization response** following skin contact *“in a substantial number of persons”* or when *“there are positive results from an appropriate animal test”.*

- **Allergic Responses: Often Dose Independent!!**

Source: alttox.org

Reproduction (& Developmental) Toxicity

Definition:

Reproductive toxicity includes the toxic effects of a substance on the reproductive ability of an organism and the development of its offspring.

Reproductive toxicity is defined as “adverse effects [of chemicals] on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring” .

Developmental toxicity means “adverse effects induced during pregnancy, or as a result of parental exposure…manifested at any point in the life span of the organism”

Source: alttox.org

Carcinogenicity

Definition:

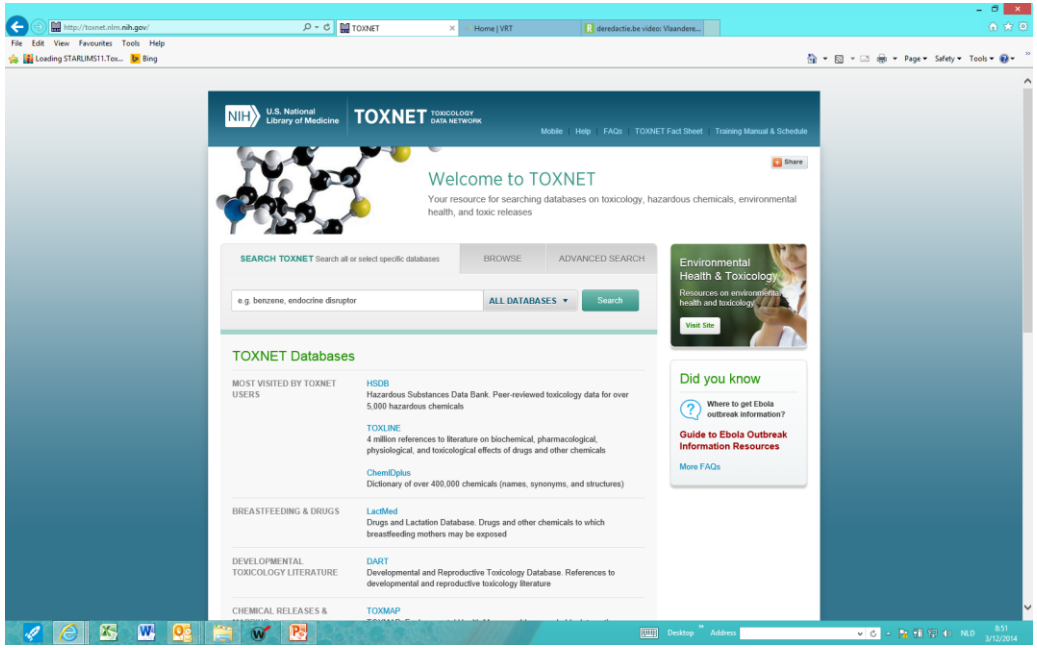
The term *carcinogen* denotes a chemical substance or a mixture of chemical substances which **induce cancer** or **increase its incidence**".

An alternate definition is that carcinogenic substances are ones that "**induce tumors** (benign or malignant), **increase** their **incidence or malignancy**, or **shorten** the **time** to **tumor occurrence** when they are inhaled, injected, dermally applied, or ingested

Carcinogens are classified according to their mode of action as *genotoxic* or *non-genotoxic* carcinogens.

DERIVING LIMITS FROM TOX DATA MOVE!

Where can we find the Toxicological Data to be used in the assessment?



http://toxnet.nlm.nih.gov
http://echa.europa.eu/
http://www.epa.gov/hpvis/
http://webnet.oecd.org/hpv/
http://www.inchem.org/
http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm

Role of Toxicologist:

- Find as much information as possible
- On all possible Toxicological End-Points
- Evaluate the weight of Evidence
- Judge the Quality of Data!!

DERIVING PDE'S FROM TOX DATA

How to evaluate the Quality and Relevancy of Tox Data?

- Duration of Studies
- Nature of Studies
- Quality of the dose-response established
- Route of Administration
- Mechanisms
- Relevance to Humans
- ...

THIS NEEDS TO BE DONE BY A TOXICOLOGIST

General Impurity Qualification

ICH Q3A / Q3B

Qualification

‘The process of **acquiring** & **evaluating** data

that establishes the **biological safety**

of an **individual impurity**

or a **given impurity profile**

at the level(s) specified.’

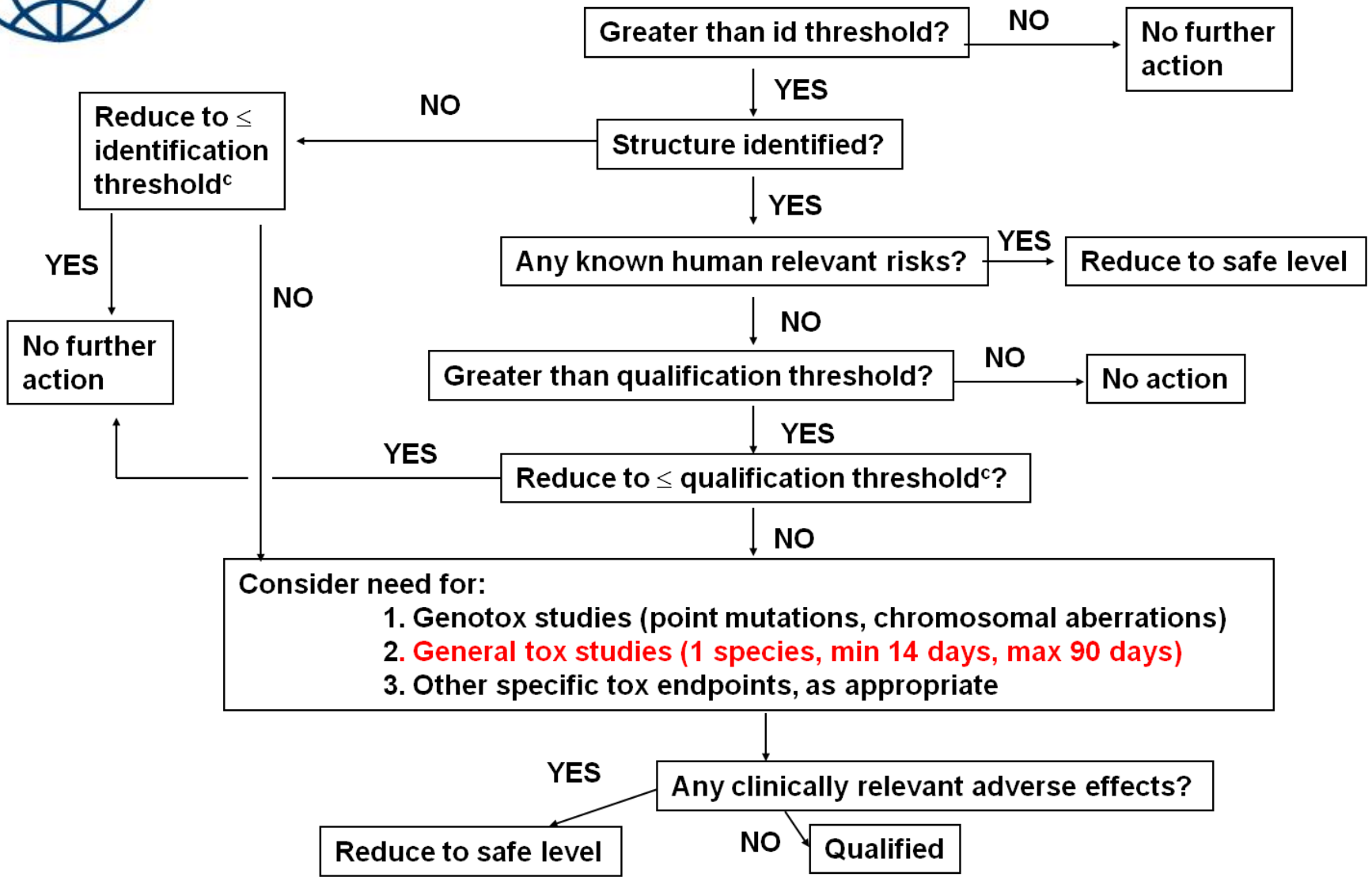
Qualification of Impurities – Basic points

- **Before** actives go into clinical trials the **impurities** present **must be qualified** in **preclinical** studies.
  - Typically includes a 14 -28 day study in rodents *(amongst others)*

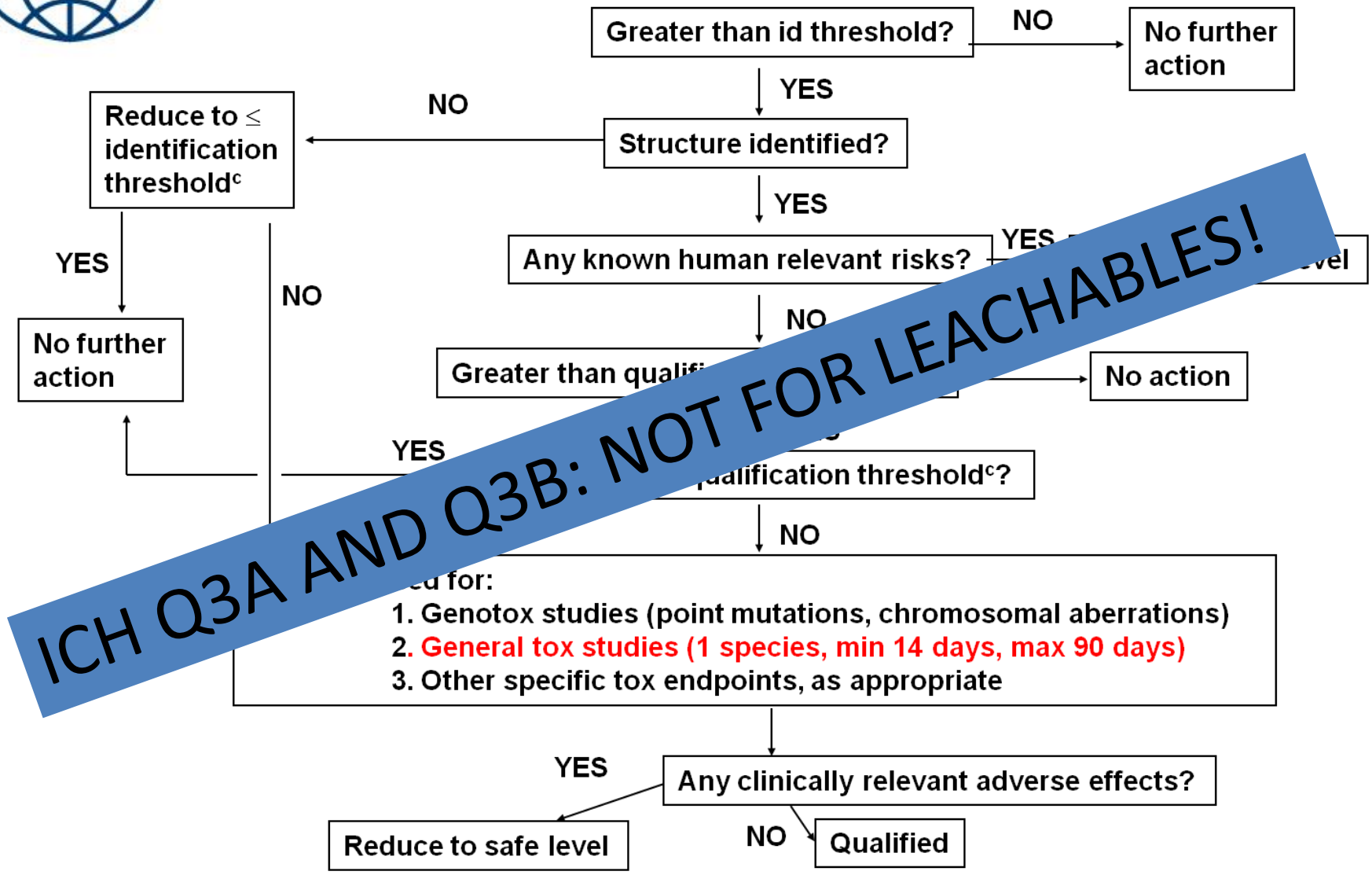
- Qualification of Impurities is described in ICH Q3A (API) & ICH Q3B (drug product)
  - **Process** described & illustrated through **Decision tree**
  - Defines thresholds for reporting, identification & qualification of impurities for Marketing Authorisation Applications
    - *E.g. For a drug dosed at up to 2g/day, the threshold for qualification for impurities is 0.15% or 1.0mg/day, whichever is lower*

- Important to note that ICH limits are not appropriate during drug development; guidance is likely to be company-specific

ICH decision tree for qualification studies



ICH decision tree for qualification studies



ICH Q3A AND Q3B: NOT FOR LEACHABLES!

Permissible Daily Exposure (PDEs)

ICH Q3C(R4): Residual Solvents

DERIVING PDE'S FROM TOX DATA

ICH Q3C Appendix 3
WHO EHC 170

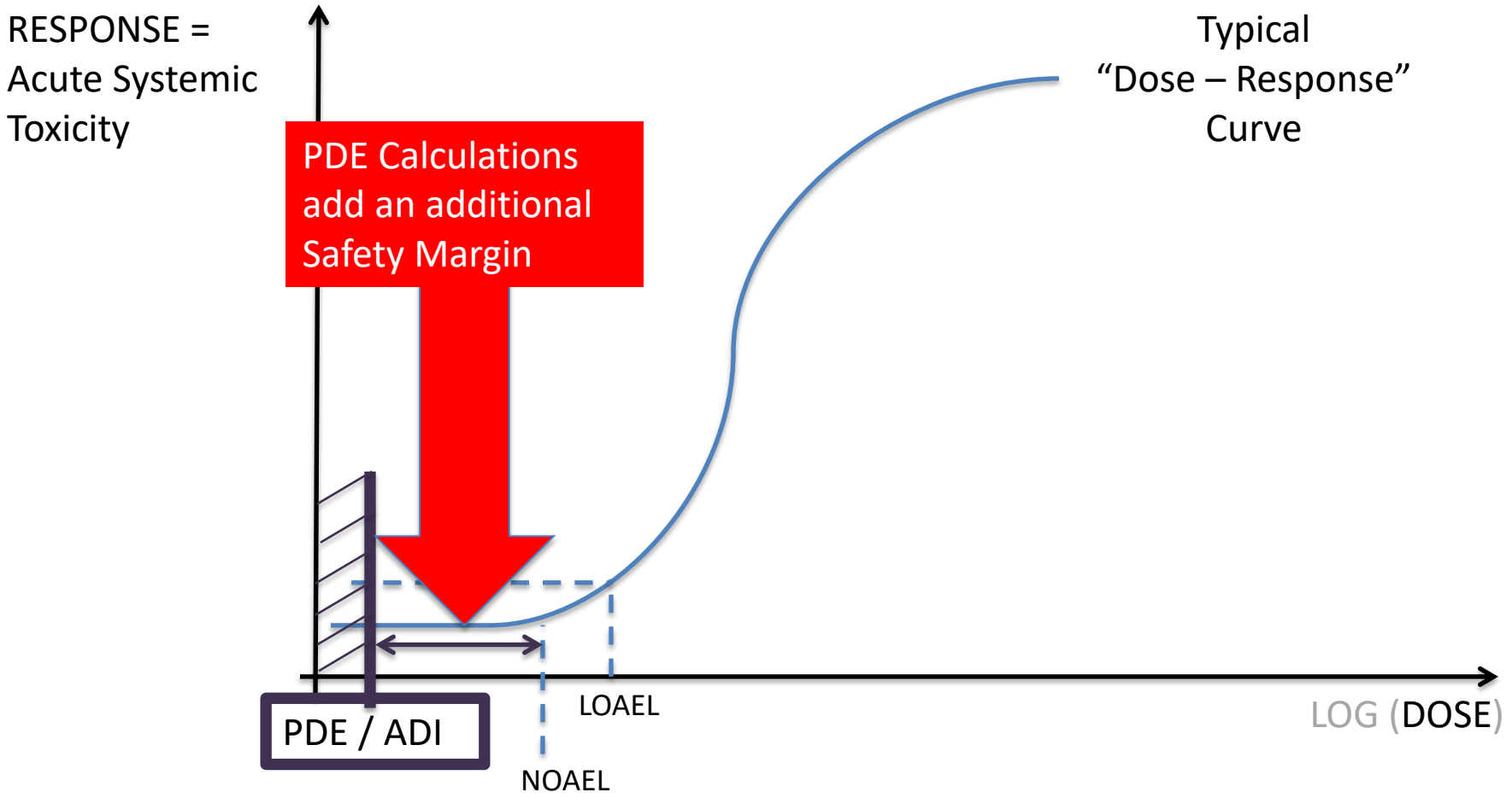
$$PDE = \frac{\text{NO(A)EL x Weight Adjustment}}{\text{F1 x F2 x F3 x F4 x F5}}$$

F1 = Variation between Species
F2 = for Variation between individual Humans
F3 = Short Duration in Animals to Chronical Human Exposure
F4 = Teratogenicity, Neurotoxicity and non-genotoxic carcinogens
F5 = 10 for using LOAEL
Sometimes **F6:** route of administration: factor 10 from oral to I.V.

REMARK: NEVER USE LD50 TO CALCULATE A PDE!
IF LD50 IS THE ONLY TOX INFORMATION, ADD LARGE ADDITIONAL SAFETY MARGINS!
Literature mentions Safety factors for LD50 as high as 2000 to obtain a NOAEL

DERIVING PDE'S FROM TOX DATA

EXAMPLE: **ACCUTE SYSTEMIC TOXICITY**



ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

TABLE 1. Class 1 solvents in pharmaceutical products (solvents that should be avoided).

Solvent	Concentration limit (ppm)
Benzene	2
Carbon tetrachloride	4
1,2-Dichloroethane	5
1,1-Dichloroethene	8
1,1,1-Trichloroethane	1500

NB – Limits for Class 1 Solvents are expressed in terms of concentration limits

ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

TABLE 2. Class 2 solvents in pharmaceutical products.

Solvent	PDE (mg/day)
Acetonitrile	4.1
Chlorobenzene	3.6
Chloroform	0.6
Cyclohexane	38.8
1,2-Dichloroethene	18.7
Dichloromethane	6.0
1,2-Dimethoxyethane	1.0
N,N-Dimethylacetamide	10.9
N,N-Dimethylformamide	8.8
1,4-Dioxane	3.8
2-Ethoxyethanol	1.6
Ethyleneglycol	6.2
Formamide	2.2
Hexane	2.9
Methanol	30.0
2-Methoxyethanol	0.5
Methylbutyl ketone	0.5
Methylcyclohexane	11.8
N-Methylpyrrolidone[1]	5.3
Nitromethane	0.5
Pyridine	2.0
Sulfolane	1.6
Tetrahydrofuran[2]	7.2
Tetralin	1.0
Toluene	8.9
1,1,2-Trichloroethene	0.8
Xylene*	21.7

ICH Q3C(R4): RESIDUAL SOLVENTS

ORGANIC IMPURITIES:

Table 3. Class 3 solvents which should be limited by GMP or other quality-based requirements.

PDE > 50 mg/day

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Mutagenic Impurities

ICH M7:

Assessment & Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk

ICH M7: DNA REACTIVE IMPURITIES

PURPOSE:

Provide a framework for

- Identification
- Categorization
- Quantification
- Control

... of mutagenic impurities to limit potential carcinogenic risk

To establish levels of Mutagenic Impurities that are expected to pose negligible Carcinogenic Risk.

ICH Q3A&B: Provide Guidance for Qualification & Control of Majority of Compounds

Limited Guidance for Impurities that are DNA Reactive

ICH M7 Complements ICH Q3A, ICHQ3B and ICH M3(R2)

ICH M7: DNA REACTIVE IMPURITIES

SCOPE:

Provide Guidance for

- New Drug Substances
- New Drug Products

During Clinical Development & subsequent Marketing Applications.

Also Applies for **New Marketing Applications** & **Post Approval Submissions, for Changes in:**

- Drug Substance SYNTHESIS
- Formulation, Composition or Manufacturing Process
- Dosing Regimen

ICH M7: DNA REACTIVE IMPURITIES

SCOPE:

LEACHABLES

» Although not intended, the safety assessment principles, outlined in ICH M7, can be used for the assessment of Leachables

EXCIPIENTS

» If used for the first time in a DP and are chemically synthesized.

EXCLUDED from SCOPE:

» Excipients, used in Existing Marketed Products

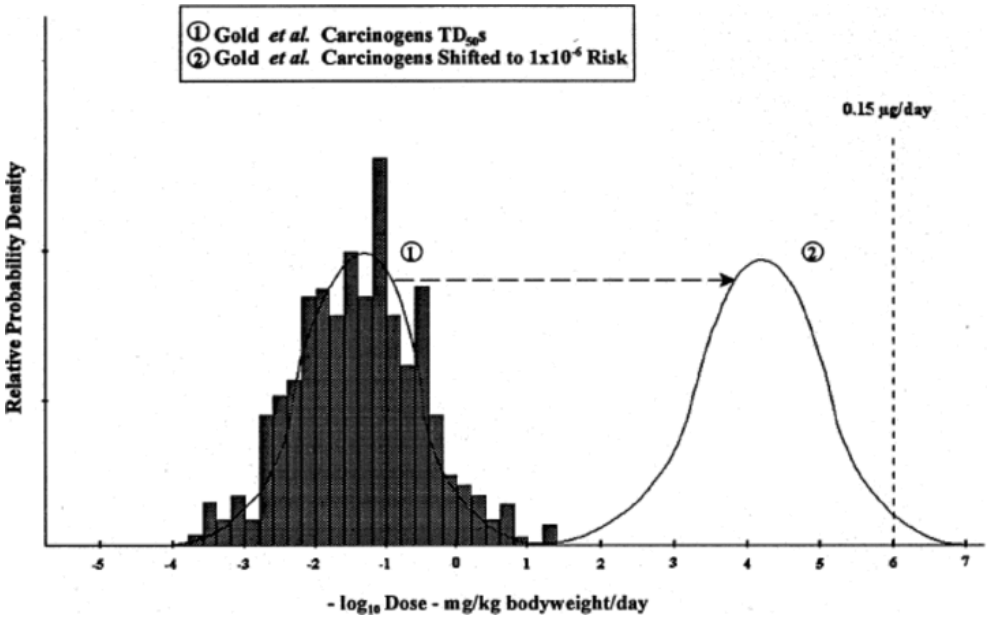
» Flavoring Agents

ICH M7: DNA REACTIVE IMPURITIES

KEY PRINCIPLES:

Limits are predicated on the basis of the **Threshold of Toxicological Concern (TTC)**

TTC based on analysis of **730 carcinogens** (genotoxic and non-genotoxic), using **linear extrapolation** from animal onco data; estimates daily exposure to 1.5µg/day for most (genotoxic) carcinogens **not likely to exceed lifetime cancer risk** of 1 in 10^5 – risk considered acceptable for pharmaceuticals as drugs have a benefit, not normally used for lifetime and precedent of benzene in Q3C.



Exceptions include aflatoxin-like, azoxy and N-nitroso compounds – need case-by-case assessment.

ICH M7: DNA REACTIVE IMPURITIES

HAZARD ASSESSMENT:

Table 1: Impurities Classification with Respect to Mutagenic and Carcinogenic Potential and Resulting Control Actions (according to Ref. 17 with modifications)

Class	Definition	Proposed action for control (details in Section 7)
1	Known mutagenic carcinogens	Control at or below compound-specific acceptable limit
2	Known mutagens with unknown carcinogenic potential (bacterial mutagenicity positive*, no rodent carcinogenicity data)	Control at or below acceptable limits (generic or adjusted TTC)
3	Alerting structure, unrelated to the structure of the drug substance; no mutagenicity data.	Control at or below acceptable limits (generic or adjusted TTC) or do bacterial mutagenicity assay; If non-mutagenic = Class 5 If mutagenic = Class 2
4	Alerting structure, same alert in drug substance which has been tested and is non-mutagenic	Treat as non-mutagenic impurity
5	No structural alerts, or alerting structure with sufficient data to demonstrate lack of mutagenicity	Treat as non-mutagenic impurity

THE DOSE-RESPONSE RELATIONSHIP –

Haber's Rule

$$C \times t = k$$

With *C = Concentration*
t = time
k = constant

This means that the toxic effect e.g. stays the same when concentration is doubled in half of the time of exposure

IMPORTANT, because this is the basis for the ***Staged Approach****, suggested in* ***ICH M7***

Remark: Not applicable to all toxicological end points – Can it be applied to general toxicity ?

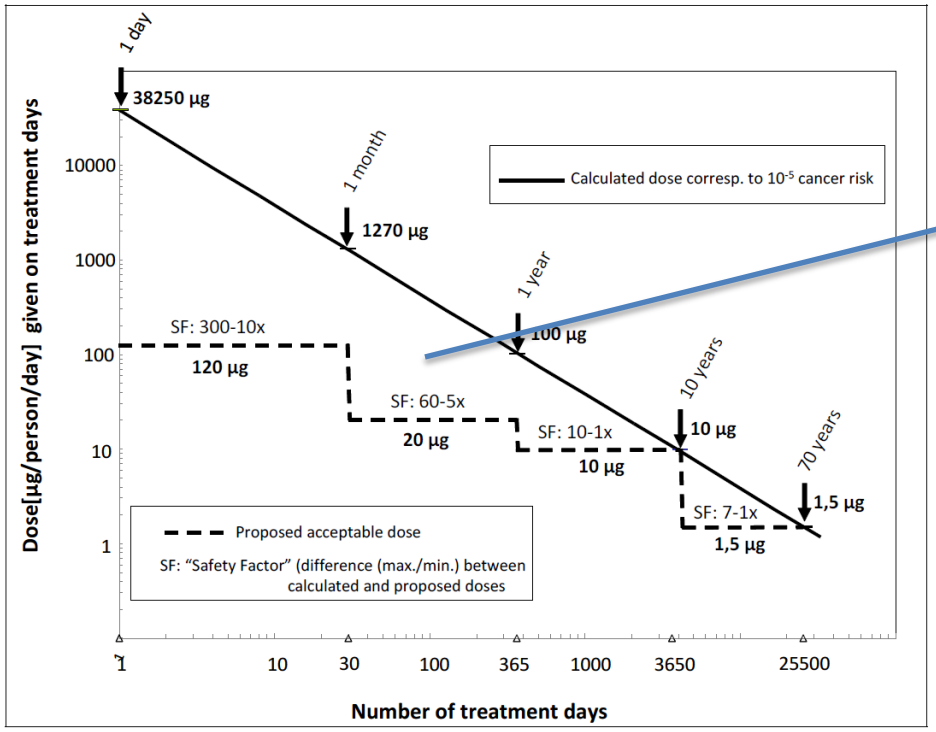
ICH M7: DNA REACTIVE IMPURITIES (draft consensus Guideline)

RISK CHARACTERIZATION:

Acceptable Intakes in relation to Less-Than-Lifetime Exposure

Table 2: Acceptable Intakes for an Individual Impurity

Duration of treatment	≤ 1 month	>1 - 12 months	>1 - 10 years	>10 years to lifetime
Daily intake [µg/day]	120	20	10	1.5



Acceptable cumulative daily dose:

1,5µg/day x 25.550 days = 38,3 mg

Uniformly distributed over total N° of exposure days

HABER's RULE:

$C \times t = k$

Compound Specific Limits

Historical Perspective

The rationale for conducting a compound-specific assessment rather than relying on a generic application of the TTC is highlighted in the EMEA guideline on the Limits of Genotoxic Impurities (EMEA, 2006) :

> *'The TTC concept should not be applied to carcinogens where adequate toxicity data (long-term studies) are available and allow for a compound-specific risk assessment.'*

The FDA draft guideline (FDA, 2008) also indicates support for such an approach and indeed goes further by indicating that the use of risk assessments based on structural similarity to known carcinogens, may also be appropriate to establish appropriate limits:

> 'When a significant structural similarity to a known carcinogen is identified, the drug substance and drug product acceptance criteria can be set at a level that is commensurate with the risk assessment specific to that of the known compound.'

Compound Specific Limits

ICH M7

Compound-specific risk assessments to derive **acceptable intakes** should be applied instead of the **TTC-based acceptable intakes** where **sufficient carcinogenicity data** exist.

For a known mutagenic carcinogen, a compound-specific acceptable intake can be calculated based on carcinogenic potency & linear extrapolation as a default approach.

PQRI –OINDP (2006):
The Threshold Approach for OINDP
*(**O**rally **I**nhaled and **N**asal **D**rug **P**roducts)*

THE PQRI-OINDP THRESHOLD APPROACH

INITIAL PQRI EFFORTS: ESTABLISH SAFETY THRESHOLDS FOR OINDPs – 2006

- Toxicologists: acquired data through extensive literature and database searches and analyses
- Chemists: acquired data by conducting extractions studies and placebo LEA studies
- Assess data and reach consensus
- Develop L & E Recommendations Document
  Submitted to FDA in 2006 for consideration in support of Regulatory Submission
- Recommendations widely used in Industry
  Not a policy/regulatory document

In 2008, PQRI started a similar approach for Parenteral & Ophthalmic DP. Expected to be finalized in ~~2015~~ → ~~2016~~ → ~~2017~~ → ~~2018~~ → 2019? 

Information, from presentation D. Paskiet, CPhI Pharma Extractables & Leachables, November 29,2012, Hyderabad.

THE **PQRI-OINDP** THRESHOLD APPROACH

SCT: **S**AFETY **C**ONCERN **T**HRESHOLD

*"Threshold below which a leachable would have a **dose so low** as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"*

PQRI for **OINDP's**: SCT = 0,15 µg/day

The SCT is not a Control Threshold, it is not a TTC

Exceptions: MBT, Nitrosamines, PNA's: as low as possible!

THE PQRI-OINDP THRESHOLD APPROACH

AET: **A**NALYTICAL **E**VALUATION **T**HRESHOLD

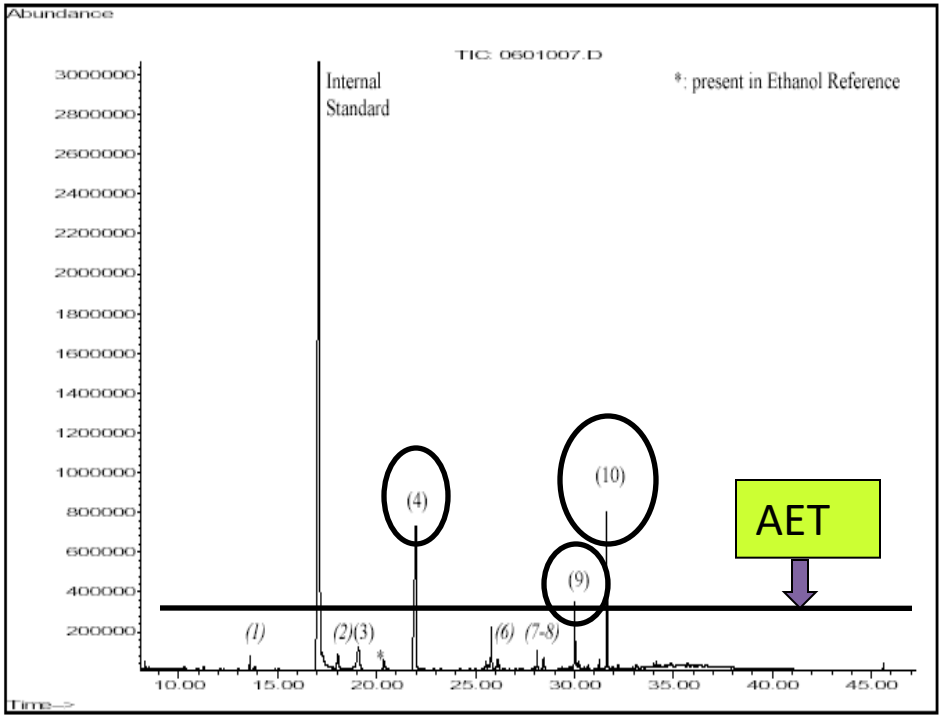
Translate SCT

into Analytical Thresholds

for Extractable Studies

Taking into account:

- *Total N° of doses / packaging*
- *Max. N° of doses administered / day*



THE PQRI-OINDP THRESHOLD APPROACH

QT: QUALIFICATION THRESHOLD

*"**Threshold** below which a given **non-carcinogenic leachable** is not considered for **safety qualification** (i.e. Tox Assessments) **unless** the leachable presents "**Structure-Activity Relationship" (SAR) concerns**."*

PQRI for OINDP's: QT = 5 µg/day

THE PQRI-OINDP THRESHOLD APPROACH

Formula used (see PQRI recommendations, *applied for QT*):

Analytical **Q**ualification **T**hreshold

$$AQT = \frac{QT}{dose/day} \cdot \frac{total\ dose}{cartridge}$$

$$AQT = \frac{5\ \mu g/day}{2\ Units/day} \cdot \frac{12\ Units}{cartridge} = 30\ \mu g\ /\ cartridge$$

FINAL AQT (incl 50% uncertainty factor) : 15 µg/cartridge

PQRI –PODP (2008 - current status):
The Threshold Approach for PODP
*(**P**arenteral and **O**phthalmic **D**rug **P**roducts)*

THE PQRI-PODP THRESHOLD APPROACH

PQRI + Parenteral and Ophthalmic Drug Products (PODP):

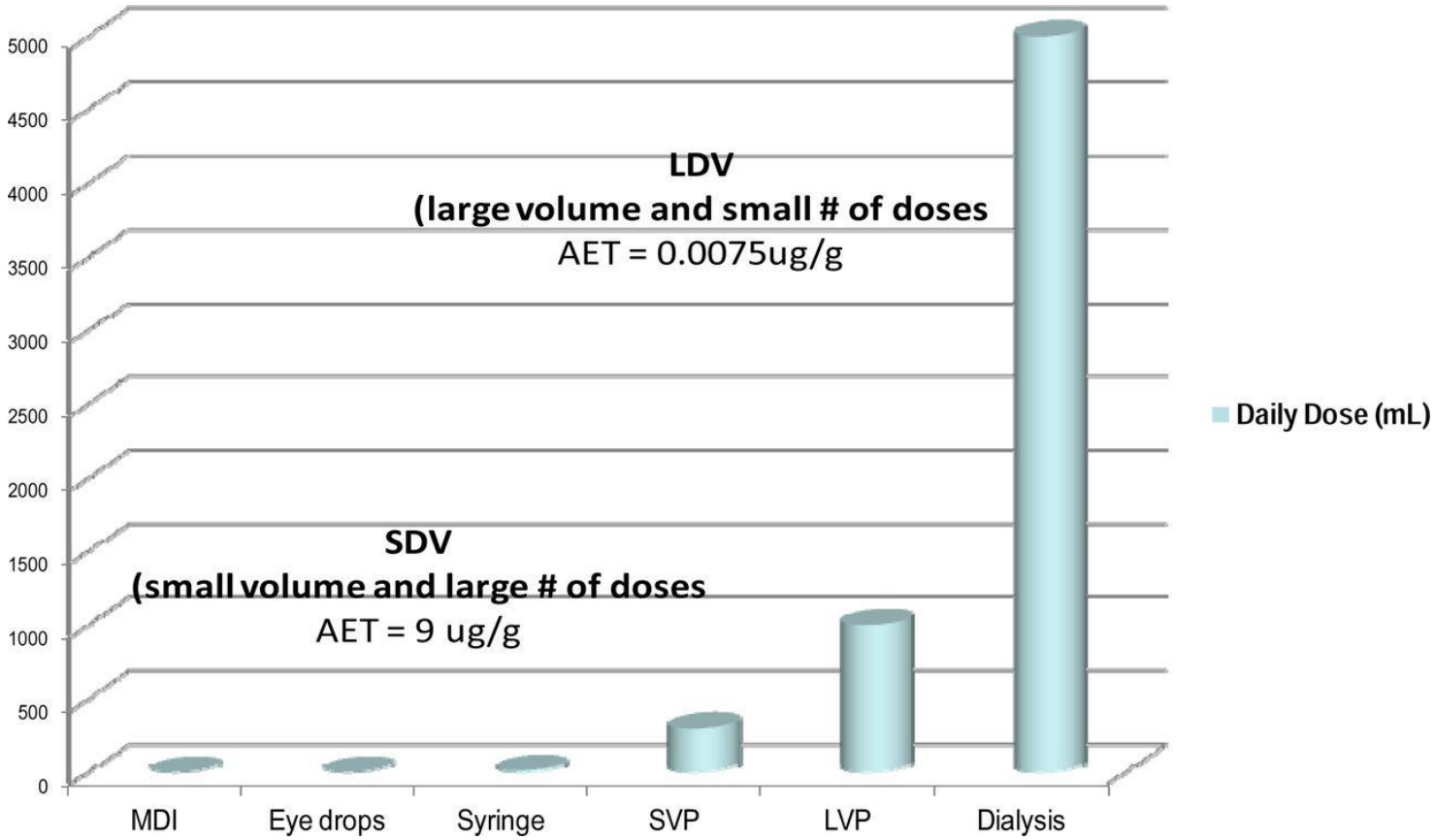
Extrapolates the OINDP threshold concepts and best practices recommendations to PODP based on following principles:

- **Threshold concepts** developed for safety qualification of leachables in **OINDP can be extrapolated** for the evaluation & safety qualification of packaging systems (such as container closure systems) of **PODP**

- **Threshold & best practice concepts** can be **integrated** into a comprehensive **process for characterizing** packaging systems with respect to leachable substances and their associated **impact on PODP safety**.

PASKET et al, PDA Journal of Pharmaceutical Science and Technology September/October 2013 vol. 67 no. 5 430-447

The effect of daily dose volume on the analytical evaluation threshold (AET).

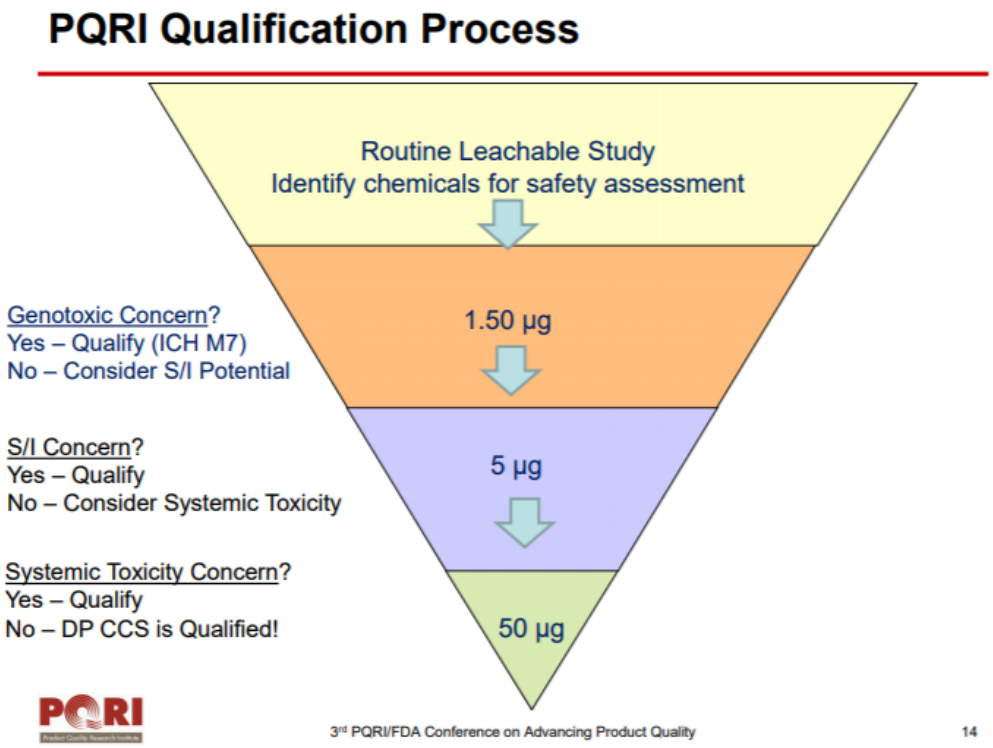


The AET is related to the safety concern threshold (SCT), which is a fixed quantity the value of the AET is inversely proportional to the daily dose volume. Thus an AET which is analytically achievable in a small daily dose volume (SDV) dosage form (e.g., metered dose inhaler, MDI) may not be achievable in a large daily dose volume (LDV) dosage form (e.g., large volume parenteral, LVP).

Paskiet D et al. PDA J Pharm Sci and Tech 2013;67:430-447

PDA Journal of Pharmaceutical Science and Technology

•Additional guidance: PQRI: Overview of Thresholds and Best Practices for Extractable and Leachables(L&E), Presentation, 3rd PQRI/FDA Conference on Advancing Product Quality Washington DC, March 2017.



=> Not duration dependent

Threshold approach - Organics

SAFETY CONCERN THRESHOLD (SCT)

"Threshold below which a leachable would have a dose so low as to present negligible safety concerns from carcinogenic and non-carcinogenic toxic effects"

Limiting Threshold, even for accute administration

PQRI for PODP

Tox Endpoint	Others	Sensitizer & Irritant	Carcinogen
Class	Class I	Class II	Class III
Threshold Level (µg/day)	50	5	1.5

THRESHOLD OF TOXICOLOGICAL CONCERN (TTC)

"Threshold of Toxicological Concern (TTC) concept was developed to define an acceptable intake for any unstudied chemical that poses a negligible risk of carcinogenicity or other toxic effects"

ICH M7 guideline

Duration of treatment	≤1 month	>1 -12 months	>1 -10 years	>10 years
Daily intake (µg/day)	120	20	10	1.5

Threshold approach - Elements

PERMITTED DAILY EXPOSURE (PDE)

ICH Q3D

- Lists PDEs in function of administration route
- PDEs can be converted
- No PDEs for typical rubber- or glass related elements

Element	Class[2]	Oral PDE µg/day	Parenteral PDE, µg/day	Inhalation PDE, µg/day
Cd	1	5	2	2
Pb	1	5	5	5
As	1	15	15	2
Hg	1	30	3	1
Co	2A	50	5	3
V	2A	100	10	1
Ni	2A	200	20	5
Tl	2B	8	8	8
Au	2B	100	100	1
Pd	2B	100	10	1
Ir	2B	100	10	1
Os	2B	100	10	1
Rh	2B	100	10	1
Ru	2B	100	10	1
Se	2B	150	80	130
Ag	2B	150	10	7
Pt	2B	100	10	1
Li	3	550	250	25
Sb	3	1200	90	20
Ba	3	1400	700	300
Mo	3	3000	1500	10
Cu	3	3000	300	30
Sn	3	6000	600	60
Cr	3	11000	1100	3

Threshold approach - Organics

ANALYTICAL EVALUATION THRESHOLD (AET)

Converting the SCT into an analytically relevant concentration

$$\text{AET} = \frac{1.5\ \mu g/\text{day}}{\text{maximum administered volume/day}}$$

Screening methods are semi-quantitative: a correction factor of 50% is introduced

$$\textit{Final AET} = \frac{AET}{2}$$

Cornerstone of all E&L testing:
Compounds detected below the (Final) AET should not be considered for toxicological assessment

Threshold approach

NARROWING DOWN THE LIST

*Max daily dose of **10 mL / day***

Class I Compounds

$$AET = \frac{50\ \mu g/day}{10\ mL/day} = 5\ mg/L$$

Class II Compounds

$$AET = \frac{5\ \mu g/day}{10\ mL/day} = 0{,}5\ mg/L$$

Class III Compounds

$$AET = \frac{1.5\ \mu g/day}{10\ mL/day} = 0.15\ mg/L$$

VOC extractables

	Result (mg/L)
COMPOUND #1	0,1
COMPOUND #2	0,2
COMPOUND #3	1,25
COMPOUND #4	2
COMPOUND #5	0,4
COMPOUND #6	0,25
COMPOUND #7	13
COMPOUND #8	0,1
COMPOUND #9	27
COMPOUND #10	0,4
COMPOUND #11	0,1
COMPOUND #12	5,5
COMPOUND #13	32,5
COMPOUND #14	1,2
COMPOUND #15	0,35

NARROWING DOWN THE LIST

*Max daily dose of **10 mL / day***

Class I Compounds

$$AET = \frac{50\ \mu g/day}{10\ mL/day} = 5\ \text{mg/L}$$

Class II Compounds

$$AET = \frac{5\ \mu g/day}{10\ mL/day} = 0{,}5\ \text{mg/L}$$

Class III Compounds

$$AET = \frac{1.5\ \mu g/day}{10\ mL/day} = 0.15\ \text{mg/L}$$

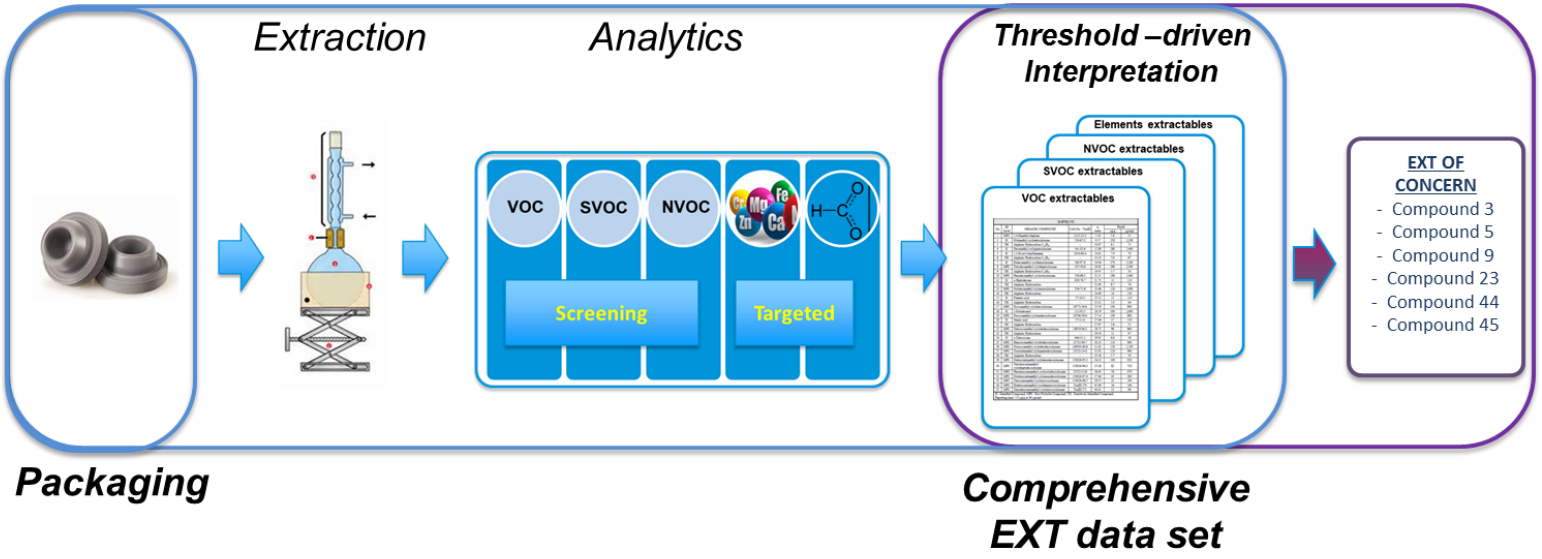
VOC extractables

	result (mg/L)	Class	Threshold (µg/day)	AET for Class (mg/L)
COMPOUND #1	0,10	I	50	5
COMPOUND #2	0,20	I	50	5
COMPOUND #3	*1,25*	III	1.5	*0,15*
COMPOUND #4	2,00	I	50	5
COMPOUND #5	0,40	II	5	0,5
COMPOUND #6	0,25	I	50	5
COMPOUND #7	*13,00*	II	5	0,5
COMPOUND #8	0,10	III	1.5	0,15
COMPOUND #9	*27,00*	I	50	5
COMPOUND #10	0,40	II	5	0,5
COMPOUND #11	0,10	III	1.5	0,15
COMPOUND #12	*5,50*	I	50	5
COMPOUND #13	*32,50*	III	1.5	0,15
COMPOUND #14	1,20	I	50	5
COMPOUND #15	0,35	II	5	0,5

EXTRACTABLES DATA

Applying threshold limit approach filters out "EXT of Concern"

- Critical information for LEA study



CONCLUSIONS

CONCLUSIONS

- Safety principles underpinned by Paracelsian principle – poison is in the dose.

- NOAEL/NOEL Levels in Accute Systemic Toxicity testing, allow to calculate PDE levels based upon AST available.
  - In case ONLY LD50 is availaible, be (very) conservative in adding an additional safety margin
  - literature additional safety factor: from 100 to 2000

CONCLUSIONS

- Conservative approach taken for Mutagenic Impurities
  - Use of Linear extrapolation to 1 in 100,000 risk, used to establish TTC – lifetime limit of 1.5 ug/day.
  - Staged Approach (based upon Haber's Rule) can be used where the identified compound is identified to be a potential carcinogen, mutagen or genotoxic compound *(and compound is not sensitizer/irritant)*
  - This concept CANNOT be used as an IDENTIFICATION THRESHOLD in Extractables & Leachables (concern for sensitizers)

CONCLUSIONS

- Conservative approach taken for Mutagenic Impurities
  - If a compound was detected with Actual Toxicity Data on Carcinogenicity/Mutagenicity, USE AVAILABLE DATA, in stead of generic approach
    - Often, this will allow you to increase the level of concern for the compound.

CONCLUSIONS

- Threshold Approach of PQRI-PODP
  - The **Identification Threshold** is either
  - **1,5 µg/day** for detected compounds in a chronic treatment application
    - as every detected compound in an E/L study could be a Carcinogen/Mutagen. Identification of the compound will either waive or confirm the concern.
  - **5 µg/day**, for detected compounds in an accute or sub-chronic treatment application
    - as every detected compound in an E/L study could be a Sensitizer/Irritant. Identification of the compound will either waive or confirm the concern.

CONCLUSIONS

Threshold Approach of PQRI-PODP

- Allows to narrow down the long list of extractable compounds, and only focus on the compounds of real concern
  - Class I (50µg/day)
  - Class II (5 µg/day)
  - Class III (1,5 µg/day)

- Compounds with [EXT]>AET: more attention!
  - Potentially to be followed up in a leachable study

CONCLUSIONS

- Final Toxicological Assessment needs to be done on the “quantitative” Leachable results

- Strong preference that it is performed by a certified Toxicologist.